What proportion of patients fail NICE criteria for continuing GLP-1 treatment beyond six months, and why?

Abstract
Glucagon-like peptide 1 (GLP-1) agonist treatment in type 2 diabetes typically improves glycaemic control and results in weight loss. The National Institute for Health and Clinical Excellence (NICE) continuation criteria are that at six months patients must have achieved at least a 3% reduction in weight and an 11mmol/mol (1%) reduction in HbA1c. The St Helens Hospital diabetes team has provided a GLP-1 service since 2007. As from August 2010, we implemented a new service structure to intensify support to patients, including monthly follow up for the first six months.

We assessed NICE continuation criteria in 43 patients who attended since the change in service structure, met NICE initiation criteria and received at least six months’ treatment. Mean age was 56 years (SD 10), diabetes duration 10 years (SD 5), baseline median weight 118kg (range 78–152), BMI 41kg/m² (range 31–60), and HbA1c 83mmol/mol (range 63–120; DCCT 9.7% [7.9–13.1]).

Thirty (70%) patients met continuation criteria. After follow up of a median 8 months (range 6–12), these patients had a median weight loss of 7.8kg (range 3–21) and a median HbA1c fall of 24.2mmol/mol (range 11–34; DCCT: 2.2% [1–5.3]). Of those failing NICE continuation criteria, 38.5% failed on weight alone, 38.5% on HbA1c alone, and 23% on both. Baseline characteristics could not predict treatment failure. Median weight loss in those failing on HbA1c alone was 8.7kg (range 2.4–12.4). Median reduction in HbA1c in those failing on weight alone was 29.7mmol/mol (2.7%).

We conclude that in our clinic most patients can continue GLP-1 treatment, but approximately 30% fail to meet NICE continuation criteria, despite clear treatment benefits.

Key words
GLP-1 receptor agonists; NICE criteria; HbA1c; weight

Introduction
The St Helens Hospital diabetes team has run a glucagon-like peptide 1 (GLP-1) service since 2007. Thus far, approximately 200 patients have been initiated on GLP-1 treatment by the team. GLP-1 stimulates insulin secretion, suppresses glucagon secretion and reduces appetite and food intake. GLP-1 treatment (exenatide) was included in the treatment algorithm in the NICE guidelines for type 2 diabetes (Clinical Guideline 87). It is indicated as a third-line agent in those of European descent with a BMI of ≥35kg/m² (making appropriate adjustments for other ethnic groups) or those with a BMI of <35 if insulin treatment is unacceptable because of occupational implications or if weight loss would benefit other comorbidities. The guidance includes criteria for the continuation of GLP-1 agonist treatment. Patients should achieve at least 3% weight loss and an 11mmol/mol (1%) fall in HbA1c in order to continue treatment beyond six months.

In 2010, NICE published their technology appraisal for the use of liraglutide, specifying the same indications and continuation criteria for GLP-1 treatment as the NICE Clinical Guideline 87 and including indications for use in dual-therapy regimens, in which case continuation criteria apply only to the aforementioned HbA1c reduction.

In 2012, NICE published their Technology Appraisal for the use of exenatide prolonged-release, with the same indications and continuation criteria for use in triple- and dual-therapy regimens as above. As from August 2010, we implemented a new GLP-1 service structure. This comprises consultant
review at 0, 3 and 6 months, group initiation of GLP-1 treatment with input from the diabetes specialist nurse (DSN) and dietitian, and DSN and dietitian reviews at 4 and 8 weeks, and at 16 and 20 weeks as needed. Following on from this initial six-month period of intensive support, the consultant reviews patients three- to six-monthly with DSN and dietitian input as needed.

**Aims**

We aimed to assess: (1) what proportion of patients fail NICE criteria for continuing GLP-1 treatment beyond six months; (2) the reasons for treatment failure; and (3) the median weight loss and HbA1c fall in those who met the continuation criteria.

**Methods**

We completed a retrospective audit of the 43 patients who commenced GLP-1 therapy from August 2010 to September 2011, and who met NICE initiation criteria and received at least six months’ treatment. We analysed the change in their weight and HbA1c and, in those failing to meet the NICE six-month continuation criteria, the reason for this failure. Although approximately 200 patients have been initiated on GLP-1 treatment by the team since 2007, we chose to include only those who were initiated on the treatment since August 2010 when we implemented the new service standards.

**Results**

Of the 43 patients included, the mean age was 56 years (SD 10) at initiation of GLP-1 therapy, and the duration of diabetes 10 years (SD 5). The baseline median weight of the group was 118kg (range 78–152), BMI 41 (range 34–60), and HbA1c 83mmol/mol (range 65–120; DCCT: 9.7% [7.9–13.1]). (Table 1.) Seventy percent of patients (n=30) met the NICE six-month continuation criteria. Of those who met the continuation criteria, after follow up of a median 8 months (range 6–12), the median weight loss was 7.8kg (range 3–21) and the median reduction in HbA1c was 24.2mmol/mol (range 11–34; DCCT: 2.2% [1–5.3]). (Table 2.) Follow-up results were taken at six-month review appointment, but due to the nature of clinic and patient rearrangements, the median time of review was 8 months (range 6–12).

Of the 13 patients who did not meet the criteria, 38.5% failed on weight alone, 38.5% failed on HbA1c alone, and 25% failed on both. Baseline characteristics were similar in responders and non-responders and thus could not predict treatment failure. The median weight loss in those failing on HbA1c alone was 8.7kg (range 2.4–12.4). The median reduction in HbA1c in those failing on weight alone was 29.7mmol/mol (range 16.5–26mmol/mol; DCCT: 2.7% [1.5–4.5]).

**Discussion**

GLP-1 therapy is a frequently used treatment for type 2 diabetes, stimulating insulin secretion, suppressing glucagon secretion and reducing appetite and food intake. NICE guidance specifies the criteria for initiation of GLP-1 therapy as well as continuation criteria for treatment beyond six months.1,2 In 2008, the Association of British Clinical Diabetologists (ABCD) launched a nationwide exenatide audit to examine the clinical usage of exenatide in the UK and to determine whether experience matched data from phase 3 trials.4 The mean baseline age was 54.9 years, duration of diabetes 8 years, HbA1c 80mmol/mol (9.47%) and weight 113.8kg. The baseline characteristics of the 43 patients included in our audit are similar – mean age 56, duration of diabetes 10 years, weight 118kg and HbA1c 83mmol/mol (9.7%). The patients in our audit were therefore a good representation of patients with diabetes across the UK.

Shyngdan et al.5 found that GLP-1 agonists reduced HbA1c levels by about 11mmol/mol (1%) in comparison with placebo in their Cochrane review comparing 17 randomised controlled trials, usually of 26 weeks’ duration. Exenatide 2mg once weekly reduced HbA1c more than exenatide 10µg twice daily.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=43)</th>
<th>Met continuation criteria (n=30)</th>
<th>Did not meet continuation criteria (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years): mean (SD)</td>
<td>56 (10)</td>
<td>57 (10)</td>
<td>56 (8)</td>
</tr>
<tr>
<td>Diabetes duration (years):</td>
<td>10 (5)</td>
<td>10 (6)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight: median (range)</td>
<td>118 (78–152)</td>
<td>119 (78–153)</td>
<td>106 (81–150)</td>
</tr>
<tr>
<td>BMI: median (range)</td>
<td>41 (31–60)</td>
<td>41 (33–53)</td>
<td>40 (31–60)</td>
</tr>
<tr>
<td>HbA1c: median (range)</td>
<td>83 (63–120)</td>
<td>81 (65–120)</td>
<td>84 (63–111)</td>
</tr>
<tr>
<td>IFCC: mmol/mol DCCT: %</td>
<td>9.7 (7.9–13.1)</td>
<td>9.6 (8.1–13.1)</td>
<td>9.8 (7.9–12.3)</td>
</tr>
</tbody>
</table>

**Table 1. Baseline characteristics of those who did and those who did not meet National Institute for Health and Clinical Excellence (NICE) continuation criteria**

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n=43)</th>
<th>Met continuation criteria (n=30)</th>
<th>Did not meet continuation criteria (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFCC: mmol/mol DCCT: %</td>
<td>2.1 (1.3–5.3)</td>
<td>2.2 (1–5.3)</td>
<td>0.8 (1.3–4.5)</td>
</tr>
<tr>
<td>Reduction in weight (kg):</td>
<td>6.3 (5.2–21)</td>
<td>7.8 (3–21)</td>
<td>1.6 (5.2–12.4)</td>
</tr>
<tr>
<td>median (range)</td>
<td></td>
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</tbody>
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**Table 2. Changes in HbA1c and weight in those who did and those who did not meet NICE continuation criteria at 6-month review**

PRACTICAL DIABETES VOL. 30 NO. 5 197
Liraglutide 1.8mg reduced HbA1c more than exenatide 10μg twice daily. Liraglutide led to improvements in HbA1c similar to those of sulphonylureas but reduced more than sitagliptin and rosiglitazone.

In the Lead-2 trial, a 26-week double-blind, placebo-controlled trial, the patients assigned to liraglutide 1.2mg in combination with metformin had a mean weight loss of 2.6kg and a mean reduction in HbA1c of 11mmol/mol (1%).

In a systematic review by Norris et al, weight loss of 1.25kg was reported and a reduction of approximately 11mmol/mol (1%) in HbA1c with 10μg exenatide twice daily, compared to placebo.

Patients included in the audit received either liraglutide 1.2mg once daily, or exenatide 10μg twice daily. Liraglutide is the treatment of choice in our clinic because of an apparent superiority shown in trials mentioned earlier, and exenatide is used if licensing criteria indicate this (eGFR 30–60). Although the number of patients included in the audit was small, it is interesting to compare the median weight loss (7.8kg) after at least six months with the weight loss found in the Lead-2 trial (2.6kg) and the Lead-4 trial (1kg). Similarly, the median reduction in HbA1c in our patients after at least six months was 24.2mmol/mol (2.2%), compared to an 11mmol/mol (1%) reduction after 26 weeks in Lead-2 and 16.5mmol/mol (1.5%) in Lead-4.

Of those who failed NICE continuation criteria, 38.5% failed on HbA1c alone, i.e. they did lose at least 3% of their baseline weight, and median weight loss in this group was 8.7kg (range 2.4–12.4). It is therefore encouraging to know that insulin detemir (Levemir) is now licensed for use with liraglutide to help achieve HbA1c target.

A strength of our study is that it is one of a few exploring the rate of failure to meet NICE continuation criteria for GLP-1 therapy. It is, however, a single-centre, retrospective audit including a relatively small number of patients. The limitations of retrospective audits are that data may be missing and selection bias is possible, although good record keeping allowed thorough data collection for this audit. Patients initiated on GLP-1 therapy from August 2010 to September 2011, who met NICE initiation criteria and received at least six months of therapy, were included, thereby limiting selection bias. Patients included in our study were a good representation of patients with diabetes in the UK, when compared to ABCD data.

The audit results conclude that the majority of our patients met NICE continuation criteria for GLP-1 therapy beyond six months. It poses the question whether the continuation criteria for GLP-1 therapy are valid. It is worth considering whether it is justifiable to stop a treatment in patients who failed on HbA1c criteria but in whom there was a median weight loss of 8.7kg, and then initiate insulin therapy which is likely to result in weight gain.

Similarly, is it justifiable to stop GLP-1 therapy in patients in whom it has resulted in a median reduction in HbA1c of 29.7mmol/mol (2.7%), but not the required 3% weight loss? As longer-term studies are being conducted in GLP-1 therapy, it will be interesting to see whether the findings impact on NICE guidance review in the future.

**References**


**Declaration of interests**

KJH has received consultancy and speaker’s fees or grants from Novo Nordisk, Astra Zeneca – BMS Alliance, Lilly Diabetes Care, Sanofi Aventis, Boehringer, Menarini, GlaxoSmithKline, Merck Sharp Dohme, and Takeda.